Research/Recherche

Multicentre clinical trials of benzimidazole-carbamates in human cystic echinococcosis (phase 2)*

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A multicentre study which constituted the second phase of trials of the efficacy of albendazole and mebendazole in human cystic echinococcosis was coordinated by WHO. A total of 112 patients from four clinical centres in Beirut, Paris, Rome and Sofia completed standardized dosage regimens of each drug and 68 patients were followed up for at least 12 months after treatment.

Albendazole was more effective than mebendazole and adverse reactions were comparable with both treatment regimens. At least 12 months is needed after treatment for an objective evaluation of the efficacy of benzimidazoles.

At present, treatment with albendazole or mebendazole should be reserved for inoperable cases of cystic echinococcosis (under strict medical supervision) and individualized according to the patient's response and the occurrence and severity of adverse reactions.

The results of a WHO-coordinated first phase (from 1982 to 1984) of a multicentre clinical trial of benzimidazolecarbamates in human *Echinococcus granulosus* and *E. multilocularis* infections (*1*) showed a low efficacy of these drags in cystic (*E. granulosus*) echinococcosis but suggested that albendazole might be more effective than mebendazole. It was also shown that treatment for 3 months may not be long enough for optimal curative efficacy and that an observation time of 6 months was too short for a definitive final evaluation of the results. It was therefore decided that in the second phase of these studies, courses of mebendazole or albendazole would be randomly allocated to patients with *E. granulosus* infections and continued for 6 months, and the follow-up time after treatment would be extended to 12 months. For ethical reasons no control group was proposed and the possibility of switching from one drug to another at any time during treatment was left to the decision of the individual clinical researchers.

Materials and methods

This WHO-coordinated study was undertaken by many physicians and research workers in four clinical centres—Beirut, Paris, Rome and Sofia during the period 1985–87 (see Acknowledgements).

Patients with cystic (*E. granulosus*) echinococcosis infection were examined and treated under a new WHO protocol[a] which proposed that patients should be randomly allocated for treatment with mebendazole (MBZ) or albendazole (ALB) according to three major criteria: age (under or over 40 years), general health status (good or not good), and location of the cysts (liver, lungs, other site or mixed). The sex of the patient and the number of cysts were not considered essential in creating a common population of patients for randomization.

A total of 176 patients were entered into the study (Table 1) and final follow-up was reported in 145. Twenty-six patients entered the study too late for the

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final observations to be recorded and the final follow-up forms for five patients were not received. Of the 145 patients for whom final follow-up forms were received, 33 were not treated long enough to be included in the final evaluation. Of these 33 patients, 13 did not return for treatment (reasons not stated), five began a new treatment regimen, seven had surgery, five were unable to tolerate the drug, two failed to comply with the treatment regimen, and one was considered cured after three months of treatment with mebendazole.

Of the remaining 112 patients, 45 were treated with MBZ and 67 with ALB (Table 1). Mebendazole was used in tablets of 650 mg, each containing 500 mg of mebendazole base. The standard dosage of MBZ progressed from 1.5 g daily in the first week, 3 g daily for the second week, to 4.5 g daily for the remainder of the 6-month period of treatment. In a few cases treatment was extended up to 8 months at the discretion of the clinical investigator. MBZ dosage was not adjusted in relation to drug levels in the plasma but doses never exceeded 4.5 g daily; children received about half of the adult dose (0.75 g initially and increasing pro rata).

Albendazole was used in tablets of 200 mg; the recommended standard daily dose was 10 mg/kg body weight. It was suggested that the drug should be given in four courses of one month with a drug-free period of 15 days between each course; the total duration of treatment therefore should have been 5½ months. Strict compliance with this regimen proved impossible since one centre had to treat all patients continuously for 3 months without drug-free intervals (these patients received ¾ of the total recommended dose) because of the necessity to shorten the hospitalization time. The daily doses of ALB varied from 0.3 g to 1.0 g per day according to the age and general status of the patients.

Of the patients who completed the treatment (Table 2), there were more females (58%) than males. The majority of patients (54%) were 40–59 years old; only 4% were below 15 years and 10% over 60 years old. The general health status was considered good at entry in 79% of the patients. Cysts in the liver alone occurred in 46%, while 29% had cysts in mixed sites; the remainder had cysts in the lungs (12%) or other organs (13%); multiple cysts (more than 10) in one organ were found in 21% of the cases. The majority of patients had had unsuccessful previous surgery (75%), and some (21%) had undergone previous treatment with a benzimidazolecarbamate drug.

In general, the patients included in this multicentre trial represented inoperable, unsuccessfully operated, or treated cases, or those with multiple cysts, i.e., conditions more severe than might reasonably be anticipated in the population at large. Neither for ethical nor for practical reasons could all patients be treated strictly according to the protocol. This explains the considerable drop-out of patients and some of the differences in the general characteristics between the two treatment groups at the end of the study.

The results of treatment were classified into three groups:

— success: a successful treatment was indicated by disappearance and/or very significant decrease in the size of *E. granulosus* cyst(s) suggesting that the lesion(s) will be absorbed or calcified in the future;
— favourable effect: these were patients with visible reductions in cyst shape and size or disappearance of some (but not all) cysts in multiple or mixed locations;
— no success: patients in this category had no visible changes in the cysts' shape, size or morphology as seen by X-ray, ultrasound and/or CT tomography; or were operated surgically during the treatment or follow-up time; or were patients with drug intolerance, change of drug, lack of compliance with the long treatment schedule, and other factors causing premature termination of treatment.

Results and discussion

The final evaluation in this trial of benzimidazolecarbamates in human cystic echinococcosis was based on 68 cases followed up for at least 12 months after treatment. Of the remaining 44 patients whose final follow-up forms were received, an evaluation was performed in 37 cases; no case was classified as "success" (Table 3).

Table 1: **Number of patients entering and completing treatment with albendazole and mebendazole, by centre**

	Entered study			Completed treatment		
Centre	Albendazole	Mebendazole	Total	Albendazole	Mebendazole	Total
Beirut	7	9	16	4	6	10
Paris	6	8	14	4	4	8
Rome	43	40	83	33	21	54
Sofia	37	26	63	26	14	40
Total	93	83	176	67	45	112

Table 2: **Characteristics of 112 patients who completed treatment for cystic (*E. granulosus*) echinococcosis**

	Albendazole	Mebendazole	Total
No. of patients	67	45	112
Age:			
6–14 years	1 (1)[a]	3 (7)	4 (4)
15–39 years	20 (30)	17 (38)	37 (33)
40–59 years	39 (58)	21 (47)	60 (54)
⩾60 years	7 (10)	4 (9)	11 (10)
Sex:			
Females	40 (60)	25 (56)	65 (58)
Males	27 (40)	20 (44)	47 (42)
General health at entry:			
Good	49 (73)	39 (87)	88 (79)
Not good	18 (27)	6 (13)	24 (21)
With cysts:			
In liver only	26 (39)	26 (58)	52 (46)
In lungs only	9 (13)	4 (9)	13 (12)
In other organs	9 (13)	5 (11)	14 (13)
Mixed localization	23 (34)	10 (22)	33 (29)
With more than 10 cysts in one organ	18 (27)	5 (11)	23 (21)
Previous surgery	50 (75)	34 (76)	84 (75)
Previous chemotherapy	19 (28)	4 (9)	23 (21)
Daily dose (g):			
Range	0.3–1.0	0.75–4.5	
Mode	0.6	4.5	
Treatment:			
3 months	33 (49)	—	33 (29)
5–6 months	34 (51)	41 (91)	75 (67)
⩾7 months	—	4 (9)	4 (4)
Length of follow-up:			
<12 months	21 (31)	23 (51)	44 (39)
⩾12 months	46 (69)	22 (49)	68 (61)
No. with ruptured cyst(s):			
In lungs	4 (6)	4 (9)	8 (7)
In other organs	1 (1)	—	1 (1)
Drug tolerance:			
Good	52 (78)	33 (73)	85 (76)
Acceptable	7 (10)	3 (7)	10 (9)
Poor	1 (1)	—	1 (1)
No evaluation	7 (10)	9 (20)	16 (14)
Reasons for early termination of follow-up:[b]			
Surgery	2 (3)	2 (4)	4 (4)
Change of drug treatment regimen	1 (1)	11 (24)	12 (11)
Loss of contact	8 (12)	9 (20)	17 (15)
Early evaluation	10 (15)	1 (2)	11 (10)

[a] Figures in parentheses are percentages of the number of patients.
[b] These patients received the full course of treatment, but follow-up was terminated before 12 months after treatment. They are not described under Materials and Methods.

Among the 46 cases treated with ALB and followed for at least 12 months, 18 (39%) gave successful results; 18 (39%) were classified as "favourable effect" and in 10 (22%) there were no visible cyst changes. Among the 22 cases treated with MBZ, 3 (14%) had successful results; 14 (64%) showed a favourable effect and in 5 (23%) there were no visible changes. The rates for the six months' mebendazole treatment are similar ($\chi^2_{(2)} = 2.03$, $P > 0.05$) to those of the three months' treatment which was used in the first phase of the clinical trial (*1*).

Mebendazole produced proportionally more successes and improvements in liver echinococcosis (80% of cases) than did albendazole (68% of cases). More

Table 3: **Evaluation of the efficacy of albendazole and mebendazole, by the length of follow-up**

	Albendazole	Mebendazole	Total
No. of patients	67	45	112
Results for patients with early termination of follow-up:	21 (100)[a]	23 (100)	44 (100)
Success	—	—	—
Favourable effect	13 (62)	6 (26)	19 (43)
No success	5 (24)	13 (57)	18 (41)
No evaluation	3 (14)	4 (17)	7 (16)
Results for patients with completed follow-up:	46 (100)	22 (100)	68 (100)
Success	18 (39)	3 (14)	21 (31)
Favourable effect	18 (39)	14 (64)	32 (47)
No success	10 (22)	5 (23)	15 (22)

[a] Figures in parentheses are percentages of the number of patients by the length of follow-up.

than half of the cysts in the lungs responded well to ALB or MBZ. Successes and improvements were also observed in a few patients with echinococcal cysts in the spleen, kidney, brain and in pelvic or abdominal cavities. Bone lesions responded rather poorly and only in patients treated with ALB (Table 4).

There was no distinct difference in the curative efficacy between a continuous three months' ALB treatment and 4 courses of treatment, each for a month, separated by 2-week intervals; but the latter schedule was much better tolerated.

Adverse effects in ALB-treated patients (18%) and in MBZ-treated ones (20%), as well as the rates of temporary withdrawal of drug or discontinuation of treatment, were similar (χ^2 test, $P > 0.05$; Table 5).

In both ALB and MBZ groups the most common adverse effect was the elevation of serum transaminases (13 cases), which led to the discontinuation of treatment in two cases (one with alcoholic liver disease, the other with a cirrhotic liver), and the temporary withdrawal of treatment in another three cases. Another common side-effect was the occurrence of gastrointestinal symptoms including severe abdominal pain (12 cases). Less common were loss of hair (5 cases), severe headache (5 cases), fever and fatigue (two cases), and sleepiness (one adolescent). The most serious complicating conditions, which led to the discontinuation of treatment, were two cases of anaphylactic shock related to the rupture of a lung cyst and of a cyst in the abdominal cavity, both after MBZ treatment. Severe urticaria and itching led to the temporary withdrawal of ALB treatment in one case. Leukopenia (two cases) and thrombocytopenia (one case) were observed only in ALB-treated patients; the latter case led to the discontinuation of treatment (Table 5).

From these observations it can be concluded that

Table 4: **Evaluation of the efficacy of albendazole and mebendazole, by location of 106 cysts in 68 patients with completed follow-up**

	Albendazole	Mebendazole	Total
Liver:	31	15	46
Success	15 (48)[a]	7 (47)	22 (48)
Favourable effect	6 (19)	5 (33)	11 (24)
No success	10 (32)	3 (20)	13 (28)
Lungs:	11	6	17
Success	4 (36)	1 (17)	5 (29)
Favourable effect	2 (18)	2 (33)	4 (24)
No success	5 (45)	3 (50)	8 (47)
Other sites:	34	9	43
Success	14 (41)	2 (22)	16 (37)
Favourable effect	5 (15)	1 (11)	6 (14)
No success	15 (44)	6 (67)	21 (49)

[a] Figures in parentheses are percentages of the number of patients by location of the cyst.

Table 5: **Adverse effects reported in patients treated for cystic echinococcosis**

	Albendazole	Mebendazole	Total
No. of patients[a]	109	83	192
No. of patients with adverse effects:	20 (18)[b]	17 (20)	37 (19)
Elevation of transaminases (with or without bilirubinaemia)	5 (5)	8 (10)	13 (7)
Abdominal pain and other gastrointestinal symptoms	7 (6)	5 (6)	12 (6)
Severe headache	4 (4)	1 (1)	5 (3)
Loss of hair	2 (2)	3 (4)	5 (3)
Anaphylactic shock	—	2 (2)	2 (1)
Leukopenia	2 (2)	—	2 (1)
Fever and fatigue	1 (1)	1 (1)	2 (1)
Sleepiness	—	1 (1)	1 (0.5)
Thrombocytopenia	1 (1)	—	1 (0.5)
Urticaria and itching	1 (1)	—	1 (0.5)
Consequences due to adverse effects:			
Lowering of daily dose	2 (2)	1 (1)	3 (2)
Temporary withdrawal of drug	3 (3)	3 (4)	6 (3)
Discontinuation of treatment	2 (2)	3 (4)	5 (3)

[a] Sixteen patients entered the study under mebendazole treatment and were later treated with albendazole.
[b] Figures in parentheses are percentages of the number of patients.

treatment with ALB or MBZ should be undertaken only if there is constant medical supervision with regular monitoring of serum transaminase levels and leukocyte and platelet counts.

Conclusions

This second phase of the multicentre clinical trials of albendazole and mebendazole in human cystic echinococcosis demonstrates that albendazole is generally more effective than mebendazole. There was no evidence that treatment with MBZ for 5–6 months was superior to the shorter course of 3 months. Treatment with ALB for a longer rather than a shorter period appeared to produce more "successes" (39.1% vs. 16.7%), but the numbers were few and the difference was not significant at the 5% level. It was confirmed that the follow-up time needed for an objective evaluation of the efficacy of benzimidazolecarbamate treatment should be at least 12 months. The response to treatment is frequently unpredictable, e.g., in one case 3 months of treatment with mebendazole produced a successful outcome, whereas in other similar cases, with 6 months of treatment, no visible changes in *E. granulosus* cysts were noted. Therefore it was concluded that at present, treatment must be individualized in each patient depending on his/her response to chemotherapy, the rate of clinical improvement, visible damage to the cysts, and the occurrence and severity of adverse reactions. Patients with liver damage should be treated with a lower dose of benzimidazolecarbamates if at all.

Chemotherapy using the available drugs should be reserved only for inoperable cases of cystic echinococcosis and conducted under strict medical supervision because of the risk of serious complications. A search for more effective drugs or better formulations of existing drugs is still needed urgently, as well as basic research on the responses of both host and parasite to chemotherapeutic intervention.

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Résumé

Essais cliniques multicentriques de traitement de l'échinococcose hydatique humaine par les carbamates de benzimidazole (phase 2)

Le Programme des maladies parasitaires de l'Organisation mondiale de la Santé a planifié et coordonné la seconde phase d'une étude destinée à évaluer l'efficacité de l'albendazole et du mébendazole dans le traitement de l'échinococcose hydatique humaine. Le traitement a été mené jusqu'à son terme chez 112 patients dans quatre centres (Beyrouth, Paris, Rome et Sofia), et les résultats ont été évalués chez 68 d'entre eux pendant 12 mois à partir de la fin du traitement, ce qui a permis de dégager les conclusions ci-après.

En général, l'albendazole a été plus efficace que le mébendazole: 18 patients sur 46 (39%) ont été traités avec succès par l'albendazole, contre 3 sur 22 (14%) par le mébendazole. L'incidence des effets indésirables a été la même pour les deux médicaments. L'essai a confirmé que, dans la plupart des cas, l'évaluation objective de l'efficacité des carbamates de benzimidazole nécessitait une période de suivi d'au moins 12 mois après la fin du traitement.

Dans l'état actuel des choses, le traitement par l'albendazole ou le mébendazole devrait encore être réservé aux cas inopérables d'échinococcose hydatique. Ce traitement exige une surveillance rigoureuse et doit être individualisé en fonction des besoins et des réactions du malade.

Reference

1. **Davis, A. et al.** Multicentre clinical trials of benzimidazole-carbamates in human echinococcosis. *Bulletin of the World Health Organization*, **64**: 383–388 (1986).